Therapeutic Agents

This invention relates to a method for treating and preventing co-morbid conditions associated with obesity and to products and pharmaceutical compositions suitable for use in such a method. More particularly, the invention relates to a method for the treatment of co-morbid conditions associated with obesity by the administration of sibutramine or a salt or a metabolite thereof and orlistat and to products and compositions containing such compounds.

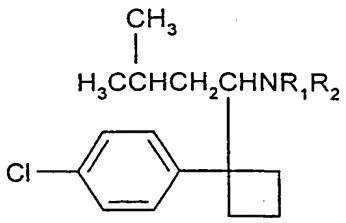
Sibutramine hydrochloride monohydrate and orlistat are both currently being developed for use in the treatment of obesity. The two compounds, however, achieve weight loss through entirely different mechanisms.

Sibutramine is a 5-hydroxytryptamine and noradrenaline reuptake inhibitor *in vivo* (Buckett, W.R., Thomas, P.C. & Luscombe, G.P. (1988). Prog. Neuro-Psychopharmacol. Biol. Psychiat. 12, 575-584 and Luscombe, G.P., Hopcroft, R.H., Thomas, P.C. & Buckett, W.R. (1989). Neuropharmacology, 28, 129-134.) Studies have shown that it reduces body weight by a dual mode of action; it decreases food intake by enhancing satiety (Fantino, M. & Souquet, A.-M. (1995). Int. J. Obesity, 19, 145; Halford, J.C.G., Heal, D.J. & Blundell, J.E. (1995). Brit. J. Pharmacol. 114, 387P; and Stricker-Krongrad, A., Souquet, A.-M. & Burlet, C. (1995). Int. J. Obesity, 19, 145.), and it increases energy expenditure by stimulating thermogenesis (Connoley, I.P., Heal, D.J. & Stock, M J. (1995). Brit. J. Pharmacol. 114, 388P; and Connoley, I P., Frost, I., Heal, D.J. & Stock, M.J. (1996). Brit. J. Pharmacol. 117, 170P).

Orlistat inhibits lipase enzymes which are responsible for breaking down ingested fat (Borgstrom, B. (1988). Biochem. Biophys. Acta. 962 (3), 308-316); as a consequence of this, unabsorbed fat is egested in the faeces.

It has been reported that orlistat should not be combined with appetite suppressants (The New York Times May 15 1997) . Surprisingly, it has now been found that co-administration of sibutramine hydrochloride monohydrate and orlistat results in beneficial effects with respect to weight-loss.

Accordingly, the present invention provides a method for the treatment of co-morbid conditions associated with obesity in a human in need of such treatment which comprises administration to the human of a therapeutically effective amount of a compound of formula I



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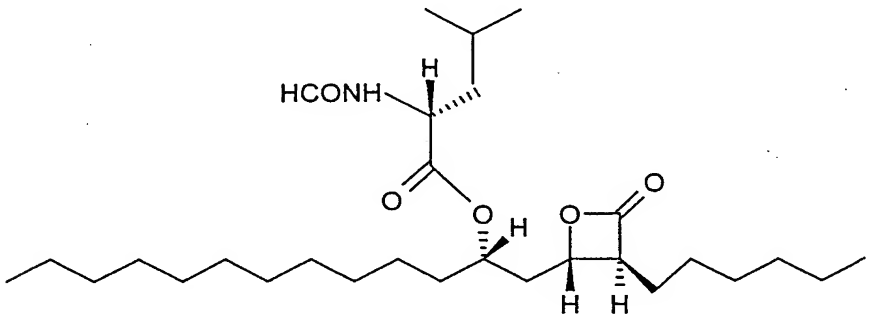
including enantiomers and pharmaceutically acceptable salts thereof, in which R_1 and R_2 are independently H or methyl, and a therapeutically effective amount of a compound of formula II



II

wherein the compound of formula I and the compound of formula II are administered simultaneously, separately or sequentially.

The present invention may provide the following advantages. Firstly, the beneficial effect achieved is greater than that achieved by the sole administration of either a compound of formula I or compound II. Secondly, a synergistic effect is achieved in which the benefit obtained by the administration of a compound of formula I and the compound of formula II to a first test group is greater than the total benefit achieved by administration of the compound of formula I to a second test group and the benefit achieved by administration of compound II to a third test group. Thirdly, when the benefit obtained after administration of either a compound of formula I or the compound II has reached a plateau, a further benefit is achieved by administering the other compound. Fourthly, lower doses of the compound of formula I and the compound of formula II may be used in the present invention thus

reducing the side-effects associated with administration of a higher dose of each compound.

The term "co-morbid conditions associated with obesity" as used in this document means medical conditions known to those skilled in the art to be associated with obesity. The term includes but is not limited to the following: diabetes including non-insulin dependent diabetes mellitus, impaired glucose tolerance, hypertension, coronary thrombosis, stroke, depression, anxiety, psychoses (for example schizophrenia), tardive dyskinesia, drug addiction, drug abuse, cognitive disorders, Alzheimer's disease, cerebral ischaemia, obsessive-compulsive behaviour, panic attacks, social phobias, eating disorders such as bulimia, anorexia, snacking and binge eating, lipid syndromes, hyperglycaemia, hyperlipidaemia, and stress in mammals particularly humans.

In addition the present invention may be useful in the treatment or prevention of metabolic diseases and conditions arising therefrom, for example non exercise activity thermogenesis and increased metabolic rate, sexual dysfunction, sleep apnoea, premenstrual syndrome, urinary incontinence including stress incontinence, hyperactivity disorders, hiatial hernia and reflux esophagitis, pain, especially neuropathic pain, weight gain associated with drug treatment, chronic fatigue syndrome, osteoarthritis and gout, cancers associated with weight gain, menstrual dysfunction, gallstones, orthostatic hypotension and pulmonary hypertension.

The present invention may be useful in preventing cardiovascular disease, and in reducing platelet adhesiveness, in aiding weight loss after pregnancy,reducing the craving to smoke and in aiding weight loss after smoking cessation. The present invention may also be useful in lowering uric acid levels and lipid levels in mammals particularly humans.

A preferred compound of formula I is N-{1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl}-N,N-dimethylamine or a salt thereof, for example the hydrochloride salt, known as sibutramine hydrochloride. A preferred form of this hydrochloride is its monohydrate, known as sibutramine hydrochloride monohydrate.

The preparation and use of compounds of formula I, such as N-{1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl}-N,N-dimethylamine and salts thereof, in the treatment of depression is described in British Patent Specification 2098602. The use of compounds of formula I such as N-{1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl}-N,N-dimethylamine and salts thereof in the treatment of Parkinson's disease is described in published PCT application WO 88/06444. The use of N-{1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl}-N,N-dimethylamine and salts thereof in the treatment of cerebral function disorders is described in US Patent 4939175. The use of N-{1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl}-N,N-dimethylamine hydrochloride in the treatment of obesity is described in European Patent Number 397831. A particularly preferred form of this compound is N-{1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl}-N,N-dimethylamine hydrochloride monohydrate (sibutramine hydrochloride monohydrate) which is described in European Patent Number 230742. The use of N-{1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl}-N,N-dimethylamine and salts thereof for improving the glucose tolerance of humans having Impaired Glucose Tolerance or Non-Insulin Dependent Diabetes Mellitus is described in published PCT application WO95/20949.

The compound of formula II has the chemical name (2*S*, 3*S*, 5*S*)-5-[(*S*)-2-formamido-4-methylvaleryloxy]-2-hexyl-3-hydroxyhexadecanoic acid lactone. It is also known as "N-formyl-L-leucine, ester with (3*S*, 4*S*)-3-hexyl-4-[(2*S*)-2-hydroxytridecyl]-2-oxetanone", (-)-tetrahydrolipstatin, tetrahydrolipistatin, and orlistat.

The extraction and use of orlistat in the control or prevention of obesity and hyperlipaemia is described in US Patent 4598089 (Hoffmann-La Roche Inc.). A process for the preparation of orlistat is described in US Patent 4983746 (Hoffmann-La Roche Inc.). A composition comprising orlistat and acarbose is described in EP638317 (Hoffmann-La Roche AGF).

It will be appreciated by those skilled in the art that compounds of formula I contain a chiral centre. When a compound of formula I contains a single chiral centre it may exist in two enantiomeric forms. The present invention includes the use of the individual enantiomers and mixtures of the enantiomers. The enantiomers may be resolved by methods known to those skilled in the art, for example by formation of

diastereoisomeric salts or complexes which may be separated, for example, by crystallisation; via formation of diastereoisomeric derivatives which may be separated, for example, by crystallisation, gas-liquid or liquid chromatography; selective reaction of one enantiomer with an enantiomer-specific reagent, for example enzymatic oxidation or reduction, followed by separation of the modified and unmodified enantiomers; or gas-liquid or liquid chromatography in a chiral environment, for example on a chiral support, for example silica with a bound chiral ligand or in the presence of a chiral solvent. It will be appreciated that where the desired enantiomer is converted into another chemical entity by one of the separation procedures described above, a further step is required to liberate the desired enantiomeric form. Alternatively, specific enantiomers may be synthesised by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents, or by converting one enantiomer to the other by asymmetric transformation. Enantiomers of secondary and tertiary amines of formula I can also be prepared by preparing the primary amine racemate, resolving this mixture into its individual enantiomers and then converting the relevant optically pure primary amine enantiomer into the desired secondary or tertiary amine product.

Preferred compounds of formula I are N-{1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl}-N,N-dimethylamine, N-{1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl}-N- methylamine, and N-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine including racemates, individual enantiomers and mixtures thereof, and pharmaceutically acceptable salts thereof. Specific enantiomers offormula I are (+)-N-{1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl}-N,N-dimethylamine, (-)-N-{1-[1-(4-chlorophenyl) cyclobutyl]-3-methylbutyl}-N,N-dimethylamine, (R)-(+)-N-{1-[1-(4-chlorophenyl) cyclobutyl]-3-methylbutyl}-N-methylamine, (S)-(-)-N-{1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl}-N-methylamine, (R)-(+)-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine and (S)-(-)-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine.

In the method of the present invention a compound of formula I and the compound of formula II may be administered concomitantly or concurrently, for example in the form of separate dosage units to be used simultaneously, separately or sequentially.

In another aspect the present invention provides a compound of formula I including enantiomers and pharmaceutically acceptable salts thereof, in which R_1 and R_2 are independently H or methyl and the compound of formula II for simultaneous, separate or sequential use for the treatment of co-morbid conditions associated with obesity.

In yet another aspect the present invention provides a compound of formula I including enantiomers and pharmaceutically acceptable salts thereof, in which R_1 and R_2 are independently H or methyl and the compound of formula II as a combined preparation for simultaneous, separate or sequential use for the treatment of co-morbid conditions associated with obesity.

In a further aspect the present invention provides a product containing a compound of formula I including enantiomers and pharmaceutically acceptable salts thereof, in which R_1 and R_2 are independently H or methyl and the compound of formula II as a combined preparation for simultaneous, separate or sequential use for the treatment of co-morbid conditions associated with obesity.

In yet another aspect the present invention provides the use of a compound of formula I including enantiomers and pharmaceutically acceptable salts thereof, in which R_1 and R_2 are independently H or methyl in the manufacture of a medicament for the treatment of co-morbid conditions associated with obesity in a patient who is also receiving treatment with orlistat.

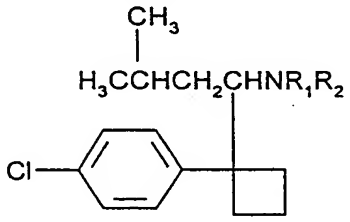
In a further aspect, the present invention provides a method of treating co-morbid conditions associated with obesity comprising the administration of an adjunctive therapy comprising a therapeutically effective amount of a compound of formula I and orlistat to a patient in need thereof.

The invention also provides the use of the above combination of drugs in the manufacture of a medicament for the treatment of co-morbid conditions associated with obesity. Additionally, it provides the combination for use in the treatment of co-morbid conditions associated with obesity.

The amount of each compound to be administered will depend on a number of factors including the age of the patient, the severity of the condition and the past medical history of the patient and always lies within the sound discretion of the administering physician but it is generally envisaged that the dosage of the compound of formula I to be administered will be in the range 0.1 to 50 mg preferably 1 to 30 mg per day given in one or more doses and more preferably 10 mg, 15 mg, 20 mg, 25 mg or 30 mg per day and most preferably 20 mg. The dosage of orlistat to be administered will be in the range of 50 to 1440 mg given in one or more doses, preferably three times daily, more preferably in the range of 120 to 720 mg and most preferably in the range of 120 to 360 mg . The compound of formula I, preferably sibutramine hydrochloride monohydrate, may be administered in any of the known pharmaceutical dosage forms. Orlistat is preferably administered orally.

In a preferred aspect of the present invention sibutramine hydrochloride monohydrate is administered once daily, preferably first thing in the morning, and orlistat is administered three times daily either with or before meals. Preferably the dose of sibutramine hydrochloride monohydrate is 20 mg or 30 mg administered once daily and the dose of orlistat is 120 mg administered three times daily either with or before meals. Most preferably the dose of sibutramine hydrochloride monohydrate is given prior to the first dose of orlistat, preferably in the range of30 minutes to 3 hours, for example 30 minutes, 1 hour, 1.5 hours, 2 hours, 2.5 hours or 3 hours, before the first dose of orlistat.

In another aspect of to the present invention there is provided a pharmaceutical composition comprising a compound of formula I



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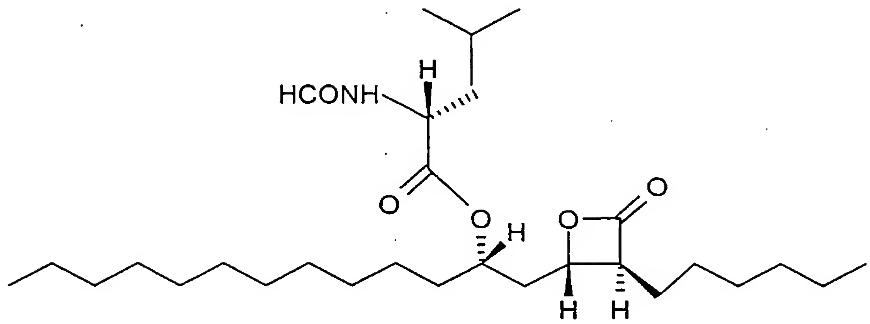
including enantiomers and pharmaceutically acceptable salts thereof, in which R_1 and R_2 are independently H or methyl, and the compound of formula II



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in conjunction with a pharmaceutically acceptable diluent or carrier.

Oral dosage forms are the preferred compositions for use in the present invention and these are the known pharmaceutical forms for such administration, for example tablets, capsules, granules, syrups and aqueous or oil suspensions. The excipients used in the preparation of these compositions are the excipients known in the pharmacist's art. Tablets may be prepared from a mixture of the active compounds with fillers, for example calcium phosphate; disintegrating agents, for example maize starch; lubricating agents, for example magnesium stearate; binders, for example microcrystalline cellulose or polyvinylpyrrolidone and other optional ingredients known in the art to permit tableting the mixture by known methods. The tablets may, if desired, be coated using known methods and excipients which may include enteric coating using for example hydroxypropylmethylcellulose phthalate. The tablets may be formulated in a manner known to those skilled in the art so as to give a sustained release of the compounds of the present invention. Such tablets may, if desired, be provided with enteric coatings by known methods, for example by the use of cellulose acetate phthalate. Similarly, capsules, for example hard or soft gelatin capsules, containing the active compound with or without added excipients, may be prepared by known methods and, if desired, provided with enteric coatings in a known manner. The contents of the capsule may be formulated using known methods so as to give sustained release of the active compound. The tablets and capsules may conveniently each contain 1 to 50 mg of the compound of formula I and 1 to 360 mg of orlistat.

Other dosage forms for oral administration include, for example, aqueous suspensions containing the active compounds in an aqueous medium in the presence of a non-toxic suspending agent such as sodium carboxy-methylcellulose,

and oily suspensions containing the active compounds in a suitable vegetable oil, for example arachis oil. The active compounds may be formulated into granules with or without additional excipients. The granules may be ingested directly by the patient or they may be added to a suitable liquid carrier (for example, water) before ingestion. The granules may contain disintegrants, eg an effervescent couple formed from an acid and a carbonate or bicarbonate salt to facilitate dispersion in the liquid medium.

The compounds of formula I and orlistat may be formulated into a composition which the patient retains in his mouth so that the active compounds are administered through the mucosa of the mouth.

Dosage forms of the compounds of formula I suitable for rectal administration are the known pharmaceutical forms for such administration, for example, suppositories with cocoa butter or polyethylene glycol bases.

Dosage forms of the compounds of formula I suitable for parenteral administration are the known pharmaceutical forms for such administration, for example sterile suspensions or sterile solutions in a suitable solvent.

Dosage forms of the compounds of formula I for topical administration may comprise a matrix in which the pharmacologically active compounds of the present invention are dispersed so that the compounds are held in contact with the skin in order to administer the compounds transdermally. A suitable transdermal composition may be prepared by mixing the pharmaceutically active compound with a topical vehicle, such as a mineral oil, petrolatum and/or a wax, e.g. paraffin wax or beeswax, together with a potential transdermal accelerant such as dimethyl sulphoxide or propylene glycol. Alternatively the active compounds may be dispersed in a pharmaceutically acceptable cream, gel or ointment base. The amount of each active compound contained in a topical formulation should be such that a therapeutically effective amount of each compound is delivered during the period of time for which the topical formulation is intended to be on the skin.

The compounds of formula I may be formulated into a composition which is dispersed as an aerosol into the patients oral or nasal cavity. Such aerosols may be

administered from a pump pack or from a pressurised pack containing a volatile propellant.

The compound of formula I may also be administered by continuous infusion either from an external source, for example by intravenous infusion or from a source of the compound placed within the body. Internal sources include implanted reservoirs containing the compounds to be infused which is continuously released for example by osmosis and implants which may be (a) liquid such as an oily suspension of the compounds to be infused for example in the form of a very sparingly water-soluble derivative such as a dodecanoate salt or a lipophilic ester or (b) solid in the form of an implanted support, for example of a synthetic resin or waxy material, for the compounds to be infused. The support may be a single body containing all the compounds or a series of several bodies each containing part of the compounds to be delivered. The amount of active compounds present in an internal source should be such that a therapeutically effective amount of each compound is delivered over a long period of time.

In some formulations it may be beneficial to use the compounds of the present invention in the form of particles of very small size, for example as obtained by fluid energy milling.

In the compositions of the present invention the active compounds may, if desired, be associated with other compatible pharmacologically active ingredients. Optionally vitamin supplements may be administered with the compounds of the present invention.

Pharmaceutical compositions incorporating both a compound of formula I and orlistat are important embodiments of the present invention. Such pharmaceutical compositions contain a therapeutically effective amount of each of the compounds. Each dosage unit may contain the daily doses of both compounds, or may contain a fraction of the daily dose, such as one-third of the doses. Alternatively, each dosage unit may contain the entire dose of one of the compounds, and a fraction of the dose of the other compound. In such case, the patient would daily take one of the

combination dosage units, and one or more units containing only the other compound.

The use of compounds of the present invention in the manufacture of pharmaceutical compositions is illustrated by the following description. In this description the term "active compound" denotes either or both compounds of the invention unless otherwise stated.

a) Capsules

In the preparation of capsules, 10 parts by weight of active compound and 240 parts by weight of lactose are de-aggregated and blended. The mixture is filled into hard gelatin capsules, each capsule containing a unit dose or part of a unit dose of active compound.

b) Tablets

Tablets are prepared from the following ingredients.

	Parts by weight
Active compound	10
Lactose	190
Maize starch	22
Polyvinylpyrrolidone	10
Magnesium stearate	3

The active compound, the lactose and some of the starch are de-aggregated, blended and the resulting mixture is granulated with a solution of the polyvinyl-pyrrolidone in ethanol. The dry granulate is blended with the magnesium stearate and the rest of the starch. The mixture is then compressed in a tabletting machine to give tablets each containing a unit dose or a part of a unit dose of active compound.

EXHIBIT 3

Enteric coated tablets

Tablets are prepared by the method described in (b) above. The tablets are enteric coated in a conventional manner using a solution of 20% cellulose acetate phthalate and 3% diethyl phthalate in ethanol:dichloromethane (1:1).

d) Suppositories (Compound of formula I only)

In the preparation of suppositories, 100 parts by weight of active compound is incorporated in 1300 parts by weight of triglyceride suppository base and the mixture formed into suppositories each containing a therapeutically effective amount of active ingredient.

Formulation 1

Hard gelatin capsules are prepared using the following ingredients:

	Quantity (mg/capsule)
Sibutramine hydrochloride monohydrate	20
Orlistat	120
Starch	200
Magnesium stearate	10
Total	350

Formulation 2

A tablet is prepared using the ingredients below:

	Quantity (mg/tablet)
Sibutramine hydrochloride monohydrate	10
Orlistat	120
Microcrystalline Cellulose	400
Silica	10

FOR EXAMINATION PURPOSES

	Quantity (mg/tablet)
Stearic acid	5
Total	545

The components are blended and compressed to form tablets each weighing 545 mg.

The advantages of the present invention may be demonstrated by animal models or clinical trials as known to those skilled in the art. Suitable animal models and methods for clinical trials may be found in :

(1). "New Antidiabetic drugs" Eds CJ Bailey & PR Flatt 1990 Smith-Gordan and company Ltd, UK

(2). "Obesity" Eds P Bjorntorp & BN Brodoff, 1992, JB Lippincott Company, Philadelphia, USA and

(3). "Obesity: Trends and Treatments" S Parker 1996 Scrip Report, PJB Publications Ltd

and references therein.

Studies are performed in which a compound of formula I is administered to a first test group, a compound of formula II is administered to a second test group, a combination of a compound of formula I and a compound of formula II is administered to a third test group with appropriate controls to eliminate the effects of the dosing vehicles used.

A statistical analysis of the effects achieved in each group provides results demonstrating the advantage of the present invention.

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